AstraZeneca	AZD2171 (cediranib)
Mechanism of Action	Vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3 tyrosine kinase inhibitor [VEGFR-1 (FLT-1)|VEGFR-2 (FLK-1/KDR|VEGFR-3 (FLT-4)] inhibitor http://www.ncbi.nlm.nih.gov/gene/2321; http://www.ncbi.nlm.nih.gov/gene/3791; http://www.ncbi.nlm.nih.gov/gene/2324
Overview	AZD2171 (cediranib) is a potent, selective, orally bioavailable inhibitor of the activity of VEGFR tyrosine kinases. Cediranib is a potent inhibitor of VEGFR tyrosine kinase activity associated with VEGFR-2 (IC_{50} < 0.001 µM) and VEGFR-1 (IC_{50} = 0.005 µM). Additional activity has been observed against the kinase associated with VEGFR-3 (IC_{50} ≤ 0.003 µM) and stem cell factor receptor (c-Kit) (IC_{50} = 0.002 µM). Cediranib is a potent inhibitor of VEGF-stimulated human umbilical vein endothelial cell (HUVEC) proliferation (IC_{50} = 0.4 nM), but does not affect basal endothelial cell growth at a > 1250-fold greater concentration. Cediranib is orally active with once-daily dosing in a range of *in vivo* test systems at 1.25 to 5 mg/kg/day producing a dose-dependent increase in the femoraltibial epiphyseal zone of hypertrophy in growing rats when dosed daily for 28 days, an observation consistent with an ability to inhibit VEGF signaling and also angiogenesis *in vivo*. In addition, cediranib was shown to inhibit VEGF-induced angiogenesis in matrigel plugs *in vivo*.
Safety/Tolerability	A comprehensive safety assessment package has been performed on AZD2171 including pivotal reproductive toxicity studies and general toxicity studies of 6 month duration in rat and non-human primate. Multiple target organs for toxicity have been identified. Of particular note are hypertension with identified sequelae in multiple organs and vasculitis in the choroid plexus. In human studies, hypertension is the primary adverse event (AE), which is an expected effect of agents that inhibit VEGF signaling. Left ventricular dysfunction, in some cases leading to cardiac failure, has been observed in patients receiving cediranib with risk factors for left ventricular dysfunction. A number of events of bleeding and hemorrhage have occurred. Fatigue, hand and foot syndrome, diarrhea, headache, nausea, vomiting, anorexia and weight loss are also commonly occurring AEs in cediranib studies. Muscle weakness, proteinuria, dry mouth, oral mucosal inflammation, reversible posterior leukoencephalopathy syndrome (RPLS) and increases in transaminases, which are sometimes associated with increases in total bilirubin, have also been observed. Thrombocytopenia, of CTC Grade 1 or 2 in the majority of cases, has been seen with monotherapy and combination cediranib treatment. Gastrointestinal perforation has been observed in patients receiving cediranib, some events have been fatal but causality could not be unequivocally assigned to Cediranib. Based on the safety, tolerability, efficacy, PK, and pharmacodynamic data available from studies with cediranib, the recommended dose in the oncology setting is 30 mg once daily when used as monotherapy. Some exceptions to this dose may be appropriate in other studies and acceptable dose levels will depend on appropriate review of risk-benefit for any proposed disease indication.
Additional Information	AZD2171 has been studied in single and multiple ascending dose studies alone and in combination with other chemotherapy agents and in Phase 2 and 3 clinical trials in cancer patients. A publicly accessible summary of the study design and outcomes of these trials can be found at www.astrazenecaclinicaltrials.com.
Suitable for and Exclusions	The reproductive toxicology package indicates that cediranib can induce effects on fetal development, therefore, the inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk-benefit and the use of appropriate contraception. Due to the known safety profile, proposals should be for diseases that require short term dosing regimens supported by current clinical experience or alternatively for diseases of severe unmet medical need where a case for tolerating potential adverse events can be made. Proposals for use in orphan indications would be particularly welcome. Studies in any field of oncology, ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD2171
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AZD2171%20or%20cediranib%20or%20recenti